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Aspergillus Lung Disease in Patients with Sarcoidosis: A Case Series and Review of the Literature

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Abstract Chronic cavitary pulmonary aspergillosis (CCPA) has been associated with advanced lung diseases. Pulmonary sarcoidosis, a granulomatous inflammatory disorder, is associated with CCPA. We identified CCPA in 2% of cases in a large cohort of sarcoidosis patients. We found a lack of response to medical treatment and poor outcome in this subgroup.

Keywords Sarcoidosis · Aspergillus · Chronic cavitary pulmonary aspergillosis

Abbreviations

ATS	American Thoracic Society
ERS	European Respiratory Society
BMI	Body mass index
$\%DL_{CO}$	Percent predicted diffusion capacity of CO in ml/mmHg/min
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
COPD	Chronic obstructive pulmonary disease
CCPA	Chronic cavitary pulmonary aspergillosis
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycosis Study Group
TLC	Total lung capacity

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Introduction

The spectrum of Aspergillus-related lung disease ranges from invasive pulmonary disease to allergic pulmonary aspergillosis in patients with hypersensitivity to Aspergillus antigens. The variety of pulmonary aspergillosis grossly depends on the host's immune status [1]. Aspergilloma is the formation of a fungus ball in a preexisting lung cavity. Another less defined lung disease related to Aspergillus is chronic necrotizing aspergillosis, which manifests as progressive lung destruction due to Aspergillus with cavity formation but without evidence of vascular invasion or disseminated disease. Chronic cavitary pulmonary aspergillosis (CCPA), on the other hand, is a recently proposed term that includes simple/complex aspergilloma and chronic necrotizing aspergillosis [2]. CCPA has been described in patients with a history of tuberculosis, COPD, pneumoconiosis, interstitial lung disease, and sarcoidosis. The exact incidence of Aspergillus-related lung disease in sarcoidosis remains unknown to date. There are few reports suggesting that these patients are at increased risk for developing fungal infections, especially Aspergillus [3].

Sarcoidosis is a systemic inflammatory disease with high incidence of lung involvement [4]. Patients may develop fungal infections, especially CCPA, leading to severe morbidity and mortality [5]. Observational case series have not identified predisposing factors for the development of CCPA, but it has been suggested that patients under immunosuppressant therapy may not have increased risk of developing such infection [6, 7]. The degree of parenchymal lung involvement in sarcoidosis seems to play a role in the development of Aspergillus lung disease. Cystic lung disease, preexisting cavitations, and bronchiectasis increase the odds for developing pulmonary aspergilloma in sarcoidosis [5, 8]. In this study we have

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attempted to identify the risk factors of developing CCPA and its outcome in a large cohort with sarcoidosis.

Methods

The study was conducted at the Sarcoidosis and Interstitial Lung Disease Center at Wayne State University, Detroit Medical Center. Approval for the use of these data was obtained from the appropriate Institutional Review Board. Records of 518 patients were reviewed and data were recorded. Ninety-seven patients were excluded because of an alternative diagnosis other than sarcoidosis. Four hundred twenty-seven patients fulfilled the criteria for the diagnosis of sarcoidosis based on ATS/ERS criteria [4]. A total of 10 patients among the 427 with confirmed sarcoidosis were identified as having Aspergillus-related lung disease. The patients were considered to have invasive pulmonary aspergillosis based on the criteria of EORTC/MSG [9]. Patients were diagnosed to have CCPA if they fulfilled the proposed criteria by Denning et al. [2]. All the patients were identified during the period of 2003 to 2010.

Results

A total of 427 patients were followed; among them a total of 10 patients were found to have pulmonary sarcoidosis with concomitant Aspergillus lung disease (Table 1). All patients fulfilled the diagnosis of chronic cavitary pulmonary aspergillosis. All patients were diagnosed with pulmonary sarcoidosis by biopsies and were African American. The major presenting symptom at the time of Aspergillus diagnosis was hemoptysis. The age range was 36-70 years (mean = 48 years). Three of the ten patients were males. The diagnosis of sarcoidosis preceded the diagnosis of Aspergillus lung disease in all cases. Chest radiography showed sarcoid stage 4. The radiological characteristics of these patients ranged from the presence of mediastinal lymphadenopathy in nine subjects, bronchiectasis in four patients, and ground glass infiltrates in seven others. All patients had evidence of cavitary lesions and aspergillomas. These changes were located on the right upper lobe in seven patients and on the left upper lobe in the other three patients. Interestingly, four cases had radiological evidence of bilateral lung involvement (Fig. 1). Pulmonary function tests (PFT) were obtained in six patients; the other four were unable to perform the test. Other characteristics found were mean FVC = 2.11 L, mean FEV_1 = 1.81 L, mean TLC = 71.5% of predicted, and mean DL_{CO} = 42.8% of predicted. Most patients were treated with prednisone, with doses ranging from 20 to 50 mg per day; in addition, two were treated with methotrexate (7.5-10 mg) weekly. Seven patients were chronic smokers, with a smoking history ranging from 10 to 20 pack-years. Four patients were frequent marijuana users.

All patients had culture-proven Aspergillus species; the cultures were obtained from sputum in one case, bronchoalveolar lavage in six cases, and tissue cultures from biopsies in three cases. Seven were *A. fumigatus,* one was *A. flavus*, and the remaining two were unidentifiable. Galactomannan levels were measured in bronchoalveolar lavage fluid and in serum of four patients, but it was never elevated.

All patients received medical treatment: voriconazole in six cases and itraconazole in the other four. Two patients on itraconazole therapy died due to massive hemoptysis and asphyxiation. Despite medical treatment, five patients continued to have hemoptysis. All five were qualified to undergo surgical treatment due to well-preserved lung function and unilateral Aspergillus lung disease. One of them died due to surgical complications. Another patient developed a persistent bronchopleural fistula after surgical lobectomy and required prolonged hospitalization. Pathological findings of lobectomy materials from this patient are shown in Fig. 2a, b. Figure 2a shows active granulomatous inflammation with destruction of the epithelial lining (H&E staining), while Fig. 2b (silver staining) shows the presence of typical Aspergillus hyphae.

Discussion

The incidence of concomitant Aspergillus-related lung disease and sarcoidosis in our series is about 2%. This incidence is a little higher than that in other series [7]. Our data suggest a higher incidence of CCPA among patients with sarcoidosis compared to other chronic lung diseases [10]. Altered lung parenchyma with advanced fibrosis and the presence of bronchiectasis has a higher association with the development of Aspergillus infection, as shown in a previous series [11]. The leading clinical presentation in our series was hemoptysis. This finding is in line with prior studies. Our findings highlight the notion that this sign should trigger further detailed investigation [12].

Interestingly, we found a higher incidence of smokers among the patients with sarcoidosis who developed CCPA. Previous studies have postulated smoking as a possible protective factor against development of pulmonary sarcoidosis [13, 14], but this hypothesis is based on the observation that most patients with sarcoidosis are non-smokers [15, 16]. In addition, four patients in our series were chronic marijuana users, a condition that has been proposed previously as a risk factor for the development or colonization with Aspergillus species and subsequent infection [17–19].

Table 1 Characteristics of the patients with CCPA and pulmonary sarcoidosis

	Age	Gender	FEV_1	Radiological findings	Sarcoid stage	Immunosuppresive therapy	Method of Aspergillus detection	Galactomannan assay	Aspergillus type	Location of CCPA	Treatment modality	Outcome
1	39	M	4.18	Bronch. MLAD Cavity	IV	Prednisone	Lung biopsy	N/A	Nontypable	RUL, LLL	Voriconazole Surgery	Alive
2	36	F	1.71	MLAD Cavities	IV	Prednisone MTX	BAL	Negative	*A. fumigatus*	LUL, Lingula	Voriconazole Surgery	Alive
3	45	M	0.67	MLAD Bullae Cavity	IV	Prednisone	BAL	N/A	*A. flavus*	LUL	Itraconazole	Alive
4	41	F	N/A	MLAD Fibrosis Cavities	IV	Prednisone	BAL	N/A	Nontypable	RUL	Voriconazole Surgery	Diseased
5	38	M	N/A	MLAD Fibrosis Cavities	IV	Prednisone	Lung biopsy	N/A	*A. fumigatus*	RUL	Voriconazole Surgery	Alive
6	51	F	N/A	MLAD Fibrosis Cavities	IV	Prednisone	Sputum culture	Negative	*A. fumigatus*	RUL	Itraconazole	Diseased
7	63	F	1.80	Bronch. Fibrosis MLAD Cavities	IV	Prednisone	BAL	N/A	*A. fumigatus*	RUL, RML	Voriconazole	Alive
8	61	F	N/A	Bronch. MLAD Cavities Fibrosis	IV	Prednisone MTX	BAL	Negative	*A. fumigatus*	LUL, RUL	Itraconazole	Diseased
9	36	F	1.08	Bronch. MLAD Fibrosis Cavity	IV	Prednisone	BAL	N/A	*A. fumigatus*	LLL	Itraconazole	Alive
10	70	F	1.47	Cavity Fibrosis	IV	None	Lung Biopsy	Negative	*A. fumigatus*	RUL	Voriconazole Surgery	Alive

M male, *F* female, *RUL* right upper lobe, *LLL* left lower lobe, *LUL* left upper lobe, *MTX* methotrexate, *bronch* bronchiectasis, *MLAD* mediastinal lymphadenopathy, *BAL* bronchoalveolar lavage

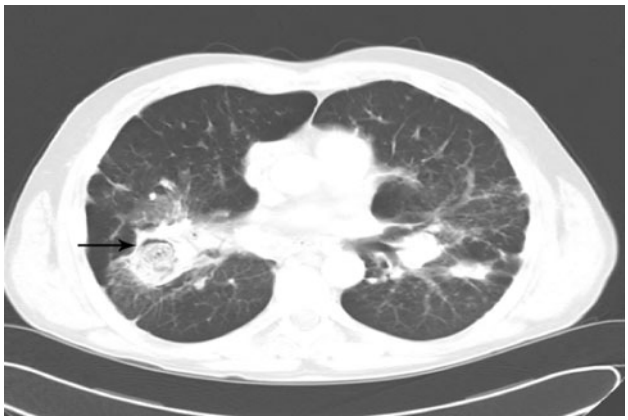

Fig. 1 Computed tomography of one patient showing bilateral Aspergillus disease and aspergilloma in the right lung with the characteristic "air crescent sign" (*black arrow*)

Recently, galactomannan antigen measurement from blood or BAL in subjects with Aspergillus infection is being used as a serological marker [20], mainly in transplant recipients [21, 22]. Interestingly, neither BAL nor serum galactomannan antigen levels were elevated in our patients. This finding is in contrast to a recent observation that the measurement of galactomannan antigen in serum, and especially in the BAL, might increase the sensitivity for diagnosis of Aspergillus infections [23]. However, the diagnostic value of galactomannan antigen detection has been investigated mostly in bone marrow recipients or other types of immunocompromised subjects with invasive Aspergillus infection. This suggests that the sensitivity of testing galactomannan might be lower in sarcoidosis patients than in immunocompromised patients.

Exact management of Aspergillus infection in patients with sarcoidosis needs further investigation. Medical management with itraconazole or more recently with voriconazole has been proposed but without any major breakthrough results [24], even though in some cases these treatments have led to improvement of symptoms and even complete resolution of radiographic and clinical pictures [25–27]. It was postulated that this favorable effect might be due to better penetration of itraconazole to the cavity compared with other treatment options. The only treatment with reasonable results is surgical resection of the aspergilloma [28]. However, there are several serious complications associated with surgery, including postoperative infection, bleeding, and the development of bronchopleural fistulas as seen in one of our patients [29]. Importantly, most patients are poor candidates in general for any surgical procedure, making careful selection of surgical candidates an essential determinant of outcome [30]. Recent reports of improved survival after surgery in this setting have attributed the results to better patient selection, increased surgeon experience, and postoperative

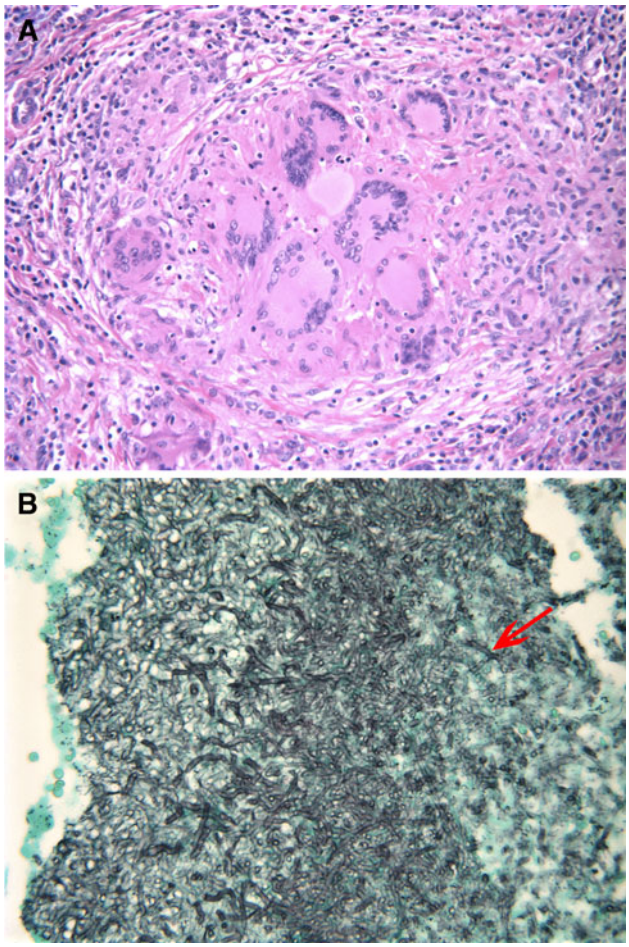

Fig. 2 Lobectomy material of patient No. 2 (see Table 1). **a** Hematoxylin and eosin (H&E) staining of lobectomy material shows the presence of noncaseating granuloma and multinucleated giant cells. Note the Langhans-type giant cells containing several nuclei arranged in a horseshoe-like pattern at the edge of the cell and around the periphery of the granuloma. **b** Histopathologic image of pulmonary semi-invasive aspergillosis. Gomori methenamine silver staining (GMS) of the same lobectomy materials. This staining gives the fungal walls a gray-black color. Note that the hyphae of Aspergillus species range in diameter from 2.5 to 4.5 μm. Aspergillus hyphae with dichotomous branching primarily at acute angles of approximately 45° (*arrow*)

management. However, there is no clear guideline to identify patients who are the best candidates to undergo such procedures [29, 31, 32]. Four of our patients who underwent surgery were treated with voriconazole for 6-18 months prior to surgical intervention. We have continued the medical treatment after surgery. We have observed in two patients that this management led to complete resolution of the hemoptysis and chronic cavitary pulmonary aspergillosis, and both remained asymptomatic 2 years after surgery. Medical treatment alone led to no resolution of Aspergillus-related infection in the nonsurgical patients, and in three subjects this infection led to death.

Voriconazole is the first-line therapy of choice for CCPA based on the Infectious Diseases Society of America (IDSA) recommendation [1]. Several studies confirmed that this medication is well tolerated and can achieve significant results [33]. However, the efficacy of this treatment and its duration in the subset of patients with sarcoidosis has not been studied. It appears that longer durations of 6-9 months are more effective [33]. In a recent study, posaconazole has been evaluated in CCPA patients; was found that patients have only a minimal response to this treatment after 1 year of therapy [34]. Comparative studies of voriconazole versus posaconazole are lacking.

Other treatment modalities have been described, including intracavitary instillation of antifungal agents like amphotericin B [35] as well as sodium or potassium bromide [36]. In cases of hemoptysis, arterial embolization of the culprit vessel has been done with some decent results [37], but all these modalities are temporary measures and not definitive. Our observation suggests using a combination of both modalities, namely, medical treatment with voriconazole and surgical intervention. This approach might be the best possible treatment, with the limitation that these patients might be poor surgical candidates. The role of pulmonary rehabilitation to try to improve lung function has not been evaluated in sarcoidosis.

The exact mechanisms underlying the development of Aspergillus lung disease in a fraction of patients with sarcoidosis remain unclear. Sarcoidosis has been considered a T helper 1 (Th1)-mediated immunity, with increased interferon γ (IFN-γ) and tumor necrosis factor (TNF-α) levels in serum and BAL fluid. One study showed variation in the profile of Th1 cytokines among sarcoidosis [38]. Both cytokines (IFN-γ and TNF-α) play an important role in immunity against fungal pathogens such as Aspergillus species [39]. It is not clear whether this subset of sarcoidosis patients who develop Aspergillus lung disease have a relatively lower level of IFN-γ to provide local immunity against the invading fungal infection. Interestingly, we have not observed any patient with the allergic type of pulmonary aspergillosis (ABPA) in our series. We have found only one reported case of ABPA in a patient with sarcoidosis after infliximab therapy [40]. It would be interesting to investigate whether local variation of Th1-type cytokines in this subset of patients plays a role in acquiring this infection.

In summary, in this case series about 2% of patients with sarcoidosis developed concomitant CCPA with poor prognosis and high mortality rate. The disease should be taken very seriously. Additional studies need to delineate the best therapeutic approach in these patients.

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